



Mode of action of some bioactive compounds with anticancer activity

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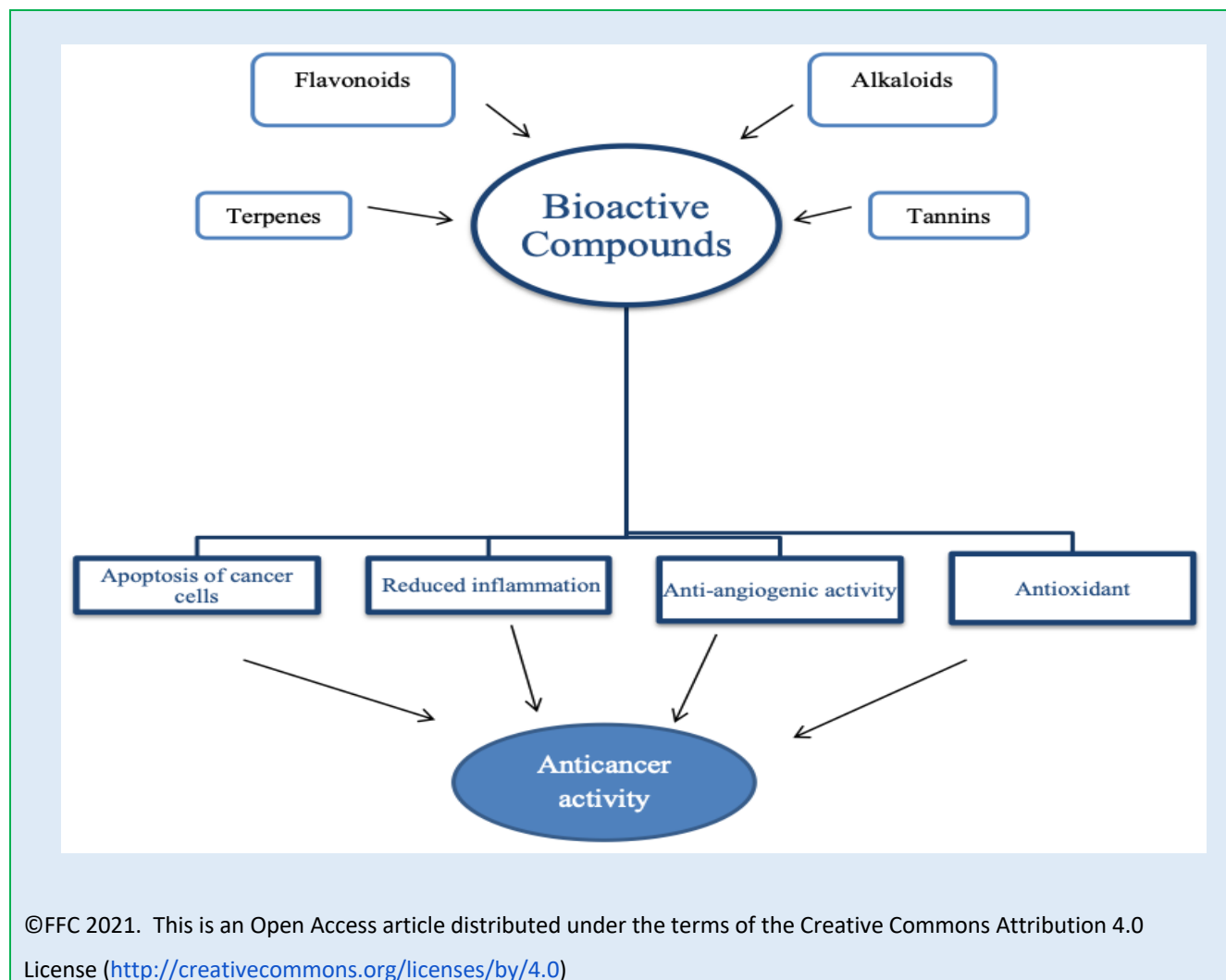
Submission Date: February 9th, 2022; **Acceptance Date:** March 21st, 2022; **Publication Date:** March 23rd, 2022

Please cite this article as: Abolanle A. A. Kayode, Grace F. Okumede and Great O. Alabi. Mode of action of some bioactive compounds with anticancer activity. *Bioactive Compounds in Health and Disease* 2022; 5(3):67-83. DOI: <https://www.doi.org/10.31989/bchd.v5i2.901>

ABSTRACT

Cancer is characterized by the development of cells that are unlike normal cells and they divide rapidly and also corrupt and destroy normal tissues in the body. Cancer cells possess the ability to spread through the body and cause damage. Cancer is caused by the mutation of DNA. The estimate of cancer cases worldwide as of 2020 has risen to 19.3 million and almost 10.0 million cancer deaths. Cancer has several means with which it sustains its growth. Cancerous action in the body involves unchecked, uncontrolled cell division and metastasis which is characterized by invading of other cells and tissues in the body. This is caused by a series of mutation in the genes of proteins that regulate the cell cycle and some other processes in the cell. These mutations suppress the ability of the cell to stop the cell cycle and promote cell division which causes continuous and uncontrolled division of cells. Bioactive compounds can be derived from plants, animals, or other sources and they have a wide range of biological and functional activities like anti-inflammatory, antiviral, anticancer, and antidiabetic activities; with the plant sources widely researched into for anticancer activities. Bioactive compounds have in recent years gained popularity in their role against cancer. This current study aims to review the mechanisms of action of anticancer activity of some of these bioactive compounds.

Keywords: anticancer, bioactive compounds, cancer, genistein, mechanism



INTRODUCTION

Cancer: Cancer is characterized by the development of cells that are unlike normal cells and they divide rapidly and also corrupt and destroy normal tissues in the body. Cancer cells possess the ability to spread through the body and cause damage [1]. Cancer is caused by the mutation of DNA. The estimate of cancer cases worldwide as of 2020 has risen to 19.3 million and almost 10.0 million cancer deaths [2]. Cancer has several means with which it sustains its growth.

Cancerous action in the body involves unchecked and uncontrolled cell division and metastasis which is characterized by invading of other cells and tissues in the body. This is caused by a series of mutations in the genes

of proteins that regulate the cell cycle and some other processes in the cell. These mutations suppress the ability of the cell to stop the cell cycle and promote cell division which causes continuous and uncontrolled division of cells [3].

There are normal genes that promote cell growth and cell division, these are the proto-oncogenes which are normal genes that promote cell growth and mitosis, whereas tumor suppressor genes repress cell growth. These proto-oncogenes are usually mutated by carcinogens to become oncogenes that produce excessive levels of growth-promoting proteins [4].

On the other hand, natural tumor suppressor genes which are transcription factors that suppress mitosis and

cell growth to allow DNA repair, are mutated in cancer making them unable to checkmate cancer. For example, p53, which is a tumor protein gene that codes for a protein that regulates the cell cycle and plays a role in cell division and cell death is mutated in cancer [5].

Following continuous mutations of proto-oncogenes and suppressor genes that permit unregulated cell growth, cancer begins to manifest [6]. Therefore cancer

cells promote characteristics or activities that favour their growth but hinder the activities that oppose their growth. These characteristics include the ability to avoid apoptosis, increase cell division, alter cell differentiation, growth-factor self-sufficient, resistance to anti-growth factors, increase cell proliferation and metastasis, lose contact inhibition and promote angiogenesis (Fig 1) [7].

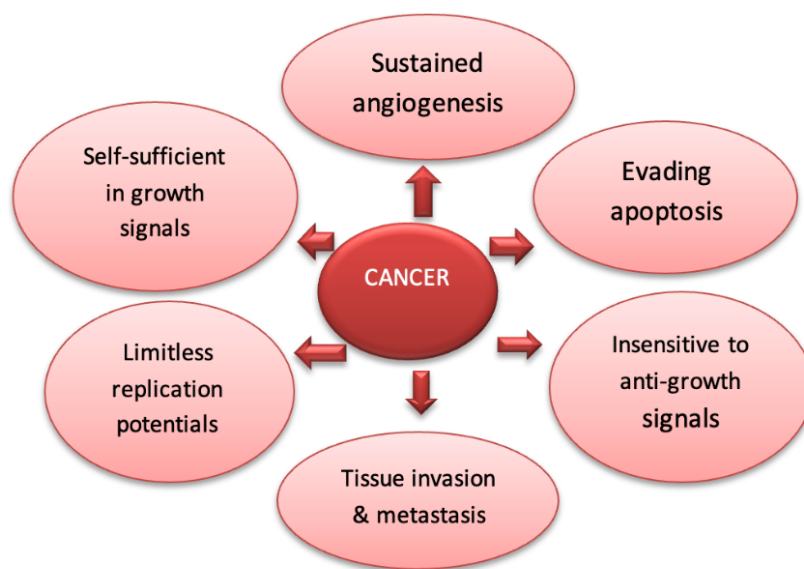


Fig 1. Mechanisms of Cancer Development [8]

Bioactive Compounds: Bioactive compounds have in recent years gained popularity in their role against cancer [8]. These bioactive agents can be grouped into different classes. Some of these bioactive compounds and their mode of action against cancer are illustrated below:

Flavonoid: Flavonoids are polyphenolic compounds that can be found in fruits, vegetables, green tea, wine, and cocoa. Some flavonoids have been shown to possess a wide variety of anti-cancer effects [9]. An example of a flavonoid with anti-cancer effect is genistein.

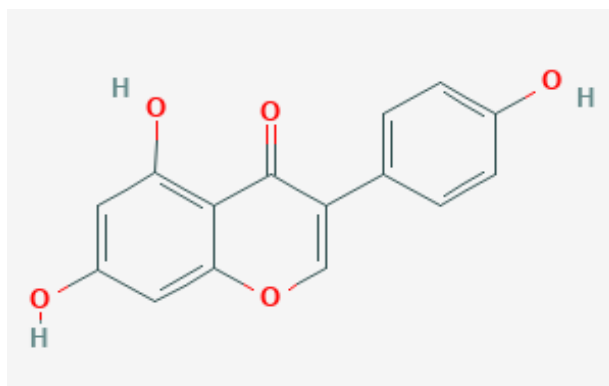


Fig 2. Chemical structure of Genistein [10]

Genistein: Genistein (4,5,7-trihydroxyisoflavone) is an isoflavone under the flavonoid family (Fig 2). It is obtained from soy products like soybeans. Other sources of genistein are dates and raisins [11]. It has been observed that in Asian countries, especially Japan and China the occurrence of breast cancer in women and prostate cancer in men was less compared to western countries like the United States. This was because these Asian countries have a higher consumption of soy products which is the richest source of genistein. It also has anti-cancer effect on other types of cancer [12].

Genistein has various mechanisms to hinder the progression of cancer. Genistein induces apoptosis of the cells by blebbing of the cell membrane, fragmentation of the cell's DNA, mitigation of attachment of cells, change of cell shape and structure, contraction of the cytoplasm, and other biological changes detrimental to the cell (Fig 3) [13].

Genistein modulates several steps critical in processes occurring in the cell. There are various means by which genistein enhances apoptosis in cancer cells. Genistein induces caspases such as caspase-3 and caspase-9 which play significant roles in the apoptosis of a cell [14].

In an *in vitro* study involving colon cancer cell, genistein triggered apoptotic cell death by inhibiting the NF- κ B pathway which mediates the induction of pro-inflammatory gene [15]. In breast cancer cell lines, genistein combined with equol, a bioactive metabolite of daidzein influenced the levels of Bax, a pro-apoptotic protein that promotes apoptosis by increasing Bax and reduced the levels of Bcl-2, an anti-apoptotic protein

whose main function is to work against Bax and hinder apoptosis [16]. In a melanoma cell line, p38 MAPK signaling pathway which responds to stress stimuli was also modulated by genistein leading to the endoplasmic reticulum of cancer cells been affected by genistein. Upregulation of GRP78, a molecular chaperon involved in protein folding and C/EBP homologous by genistein, increased endoplasmic reticulum stress resulting in apoptosis [17].

In hepatocellular carcinoma, genistein discontinued the supply of oxygen to cancer cells by inactivating a glucose transporter in the cell called GLUT 1 by down-regulating hypoxia-inducible factor-1 α thereby mitigating aerobic glycolysis in the cells which in turn suffocated the cancer cell eventually leading to apoptosis [18]. Genistein caused the overactivity of Calpain 1 which led to the lysosomal membrane being very permeable thereby triggering the release of cathepsin B and DNase II resulting in damaged DNA of the cancer cells and therefore apoptosis in human breast cancer MCF-7 cell lines [19].

The proliferation of cancer cells usually depends on some inflammatory markers. Therefore, in an *in vitro* study on human keratinocytes (HaCaT cell line), genistein suppressed tumor necrosis factor- α (TNF- α)-induced nuclear factor- κ B (NF- κ B) translocation [20]. It also mitigated the phosphorylation of I κ B kinase- α/β and induced the activation of caspase 8 by promoting the attachment of Fas/TNF, a death receptor to FasL/TNFR1, the combination of this ligand to the receptor will trigger apoptotic reactions [21].

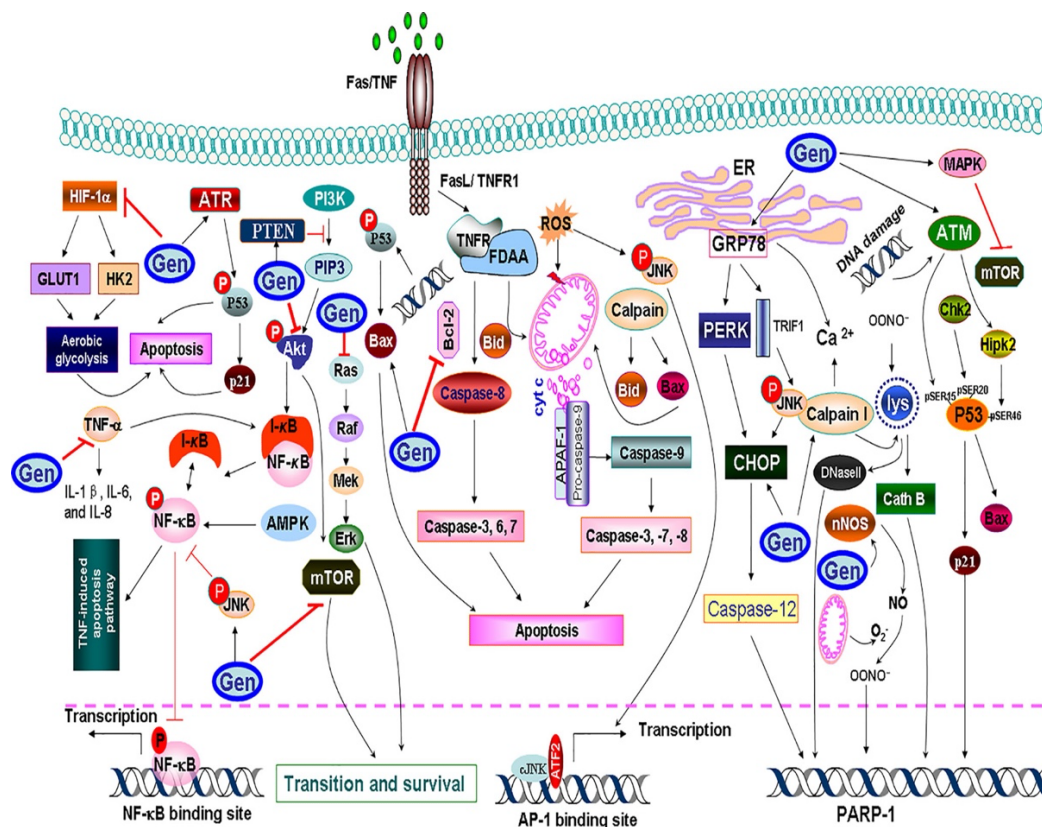


Fig 3. Genistein’s mechanism of inducing apoptosis in cancer cells [21]

Asides from inducing cell death in cancer cells, genistein utilizes other mechanisms like halting or reducing vascularization of the cancer-ridden area thereby starving cancer cells. Cancer cells also need supply of blood and nutrients, therefore anything that hinders them from receiving the required nutrients can be a promising method to alleviate the rampage of cancer. The development of new blood vessels is known as angiogenesis. Genistein has been shown in a colon cancer study to possess antiangiogenic properties where it was implicated in the hindrance of vascular endothelial growth factor (VEGF) [22]. Vascular endothelial growth factor is a signalling protein that promotes the growth of new blood vessels, therefore by inhibiting the activities of VEGF, genistein hinders angiogenesis. Genistein also hindered angiogenesis by down-regulating matrix metalloprotease-2 (MMP-2), matrix metalloprotease-9 (MMP-9) expression, and urokinase plasminogen activator. It enhanced components that inhibit

angiogenesis such as angiostatin, plasminogen activator inhibitor-1, thrombospondin-1, and endostatin. Activation of these inhibitors of vascularization hindered the formation of new blood vessels. This shows that genistein by hindering the growth of blood vessels can stop the growth of cancer cells [23].

Halting of the cell cycle is another mechanism by which genistein mitigates cancer. Cancer cells undergo proliferation because they need to grow and divide. Genistein prevented the multiplication of the cells by halting the cell cycle. In human gastric carcinoma, genistein inhibited the growth of cancer cells by halting the cell cycle succession at G2-M thereby stopping the division of the cells [22].

Genistein also initiated the activation of the ATM/ATR-p53-p21 signaling pathway via the phosphorylation of this pathway leading to a halt in the cell cycle (Fig 4). Platelet-derived growth factor that stimulates cells to begin the cell cycle was inhibited by

genistein. Genistein also regulated several regulatory proteins in the cell cycle by modulating their expression in the cell [21]. For instance, in esophageal carcinoma cells, genistein down-regulated the expression of Cdc25C which is a drive for cell cycle. Genistein downregulated cyclin which activates cyclin-dependent kinase by inhibiting the binding of cyclin to cyclin-dependent kinase which in turn inhibited the expression cyclin-dependent kinase. Another way genistein hindered cyclin-dependent kinase was by upregulating the expression of

its inhibitor p21WAF/CIP1 which hinders cyclin-dependent kinase from binding to cyclin-cyclin-dependent kinase complexes before inhibiting their activity [24]. Aside from these, genistein triggered cell arrest by modulating mitogen-activated protein kinase (MAPK) thereby down-regulating cyclin, Cdc25C, and cyclin-dependent kinase. Genistein also inactivated cyclin-dependent kinase by activating Chk1 and Chk2 which are checkpoint kinases that can cause cell cycle arrest [25].

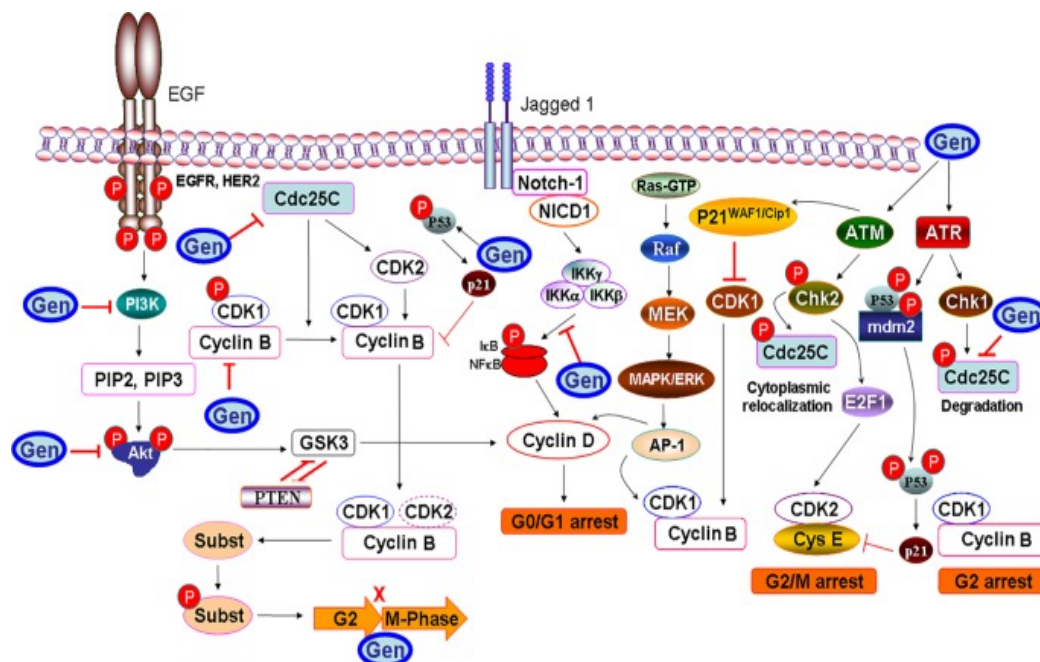


Fig 4. Mechanism by which Genistein halts cell cycle of cancer cells [21]

Furthermore, cancer cells depend on their ability to spread to other regions. Studies have shown that genistein has the potential to stop metastasis which is the spread of cancer cells. Genistein inhibited several factors implicated in cancer cells metastasis such as COX-2, matrix metalloproteinase-9, Ang-1, vasodilator-stimulated phosphoprotein, and vascular endothelial growth factor. Genistein reduced the ability of the cells to adhere together by reducing the expression of focal adhesion kinase (FAK) [21]. Genistein also reduced the expression of an epithelial-to-mesenchymal transition transcription factor. In an in vitro study involving melanoma cells, genistein down-regulated some other

factors like vinculin, p-paxillin, α -actinin and tensin-2 [26].

This shows that the mechanisms by which genistein acts in its anticancer effect are quite vast and unlike most anticancer drugs or treatment that are more specific. Therefore genistein treatment is a promising path in fighting against cancer.

Other flavonoids that have shown considerable anticancer properties are cyanidin, luteolin, peonidin, malvidin, daidzein, pelargonidin, delphinidin, taxol, and vinblastine [9].

Alkaloid: Alkaloids are organic nitrogen derivatives. They can be found in coffee, cacao, and teas like green tea.

These alkaloids possess anticancer effects. An example of an alkaloid exhibiting anticancer effect is berberine.

Berberine: Berberine is an isoquinoline protoalkaloid (Fig 5). Other isoquinoline alkaloids are columbamine dehydrocorydaline, palmatine, jatrorrhizine and epiberberine, and coptisine [27]. Berberine can be found

in plants and herbs like tree turmeric (*berberis aristata*), goldenseal (*hydrastis canadensis*), oregon grape (*berberis aquifolium*), barberry (*berberis vulgaris*), huanglian (*coptidis rhizome*), European barberry, greater celandine, and phellodendron [28].

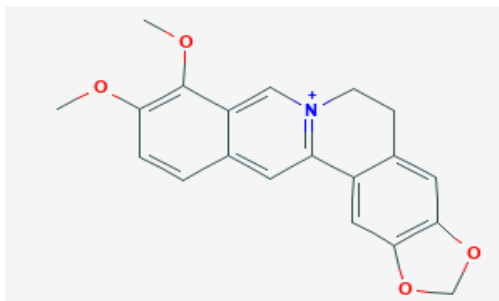


Fig 5. Chemical structure of Berberine [29]

Berberine has various mechanisms of exhibiting its anti-cancer properties such as halting metastasis and cell cycle of cancer cells, anti-inflammatory and anti-oxidant activities, inhibiting angiogenesis and reduction of transcription factors (Fig 6). Cancer cells utilize cytokines as a means of contaminating surrounding cells. Berberine however stomps on the inflammatory path of cancer cells by downregulating pathways that can further fuel inflammation like the caspase-1/IL-1 β signaling pathway [32]. Berberine also stopped cancer cells metastasis in uterine cancer cell lines by reducing the expression of transcription factor snail-1 [33] and directly affecting microRNAs. MicroRNAs have been implicated at the early and developmental stages of cancer cells. In some cancer cells such as hepatoma cells of the liver, berberine modulated the transcriptional activation of p21 and GADD45 α by up-regulating the expression of miR-23a [34]. The multiplication and migration of cancer cells were inhibited by berberine through the down-regulation of GRP78 expression [35].

Berberine induced Nrf2 activation, decreased oxidized LDL-induced inflammation by regulating the AMPK/mTOR signaling pathway thereby reducing inflammation [36]. Anti-inflammatory activities of berberine were also exerted by stimulating the AMPK α -

SIRT-1-PGC-1 α signaling pathway and inhibiting the mitogen-activated protein kinase 4 -SAPK/JNK-C-JUN. Down-regulation of TNF α and IL-6 was also observed in the treatment with berberine [37].

Berberine may also serve as an anti-oxidant because it increased the activities of catalase and glutathione peroxidase enzymes in melanoma cells [38]. Some studies also show that berberine reduced oxidative injury by suppressing reactive oxygen species through the inhibition of mTOR, P13K, and AKT pathways which could increase the risk of cancer [39].

Angiogenesis was hindered by berberine in cancer by downregulating the expression of vascular endothelial growth factor (VEGF), IL-2, IL-6, and TIMP which play key roles in the formation of new blood vessels [40]. Cancer utilizes these blood vessels to get nutrients that support the growth of cancer cells if not mitigated. In an *in vitro* study on 22RV1 human prostate cancer cell, berberine reduced the expression of matrix metalloproteinase-2 (MMP2) and matrix metalloproteinase-9 (MMP9) by inhibiting the COX-2, PGE2-JAK2, and STAT3 signaling pathways. Inhibition of the expression of MMP-2 and MMP-9 was also done by downregulation of TGF- β 1. These along with the targeting of ephrin-B2 hindered cell spreading and proliferation [41].

In human gastric, colon, liver and lung cancer cells, berberine enhanced apoptosis in cancer cells preventing the progression of the cancer cells. It stimulated cell death by increasing the activity of various factors in the cell leading to a series of reactions eventually causing the death of the cells. Berberine activated caspase-3 thereby inhibiting the expression of Bcl-2 and enhancing the expression of caspase-8 and caspase-9 [42]. The caspases were activated by berberine through an elevated cytochrome C level, AMPK activation, and elevated production of ROS. The activation of JNK and p38 also increased p53 phosphorylation promoting the entry of Bax and Bim into mitochondria, resulting in the heightened permeability of the mitochondrial membrane. All these eventually leading to apoptosis. Berberine also induced the expression of ATF3 protein by increasing the transcription of p53 thereby promoting cell apoptosis [43].

The cell cycle in cancer cells was also halted by berberine, this hindered the growth and multiplication of

the cell thereby slowing down or stopping their proliferation. Berberine achieved the inhibition of the cell cycle by modulating cyclin, therefore, inhibiting cyclin-dependent kinase (CDK4) expression. Berberine utilized this mechanism in melanoma cells to stop cell growth by modulating P13K, Akt and p38 activation thereby up-regulating p21 and p53 expression resulting in the arrest of the G2/M phase in the cell cycle Berberine prevented the transition from G1 phase to S phase by inhibiting the phosphorylation of Rb protein, which stopped the detachment of E2F, a transcriptional activator from Rb [38]. These mechanisms are represented in Fig 7 and through all these mechanisms berberine can be used as an anticancer agent although more research needs to be carried out.

Other alkaloids that possess anticancer properties include evodiamine, piperine, sanguinarine, tetrandrine, noscapine, and mutrine.

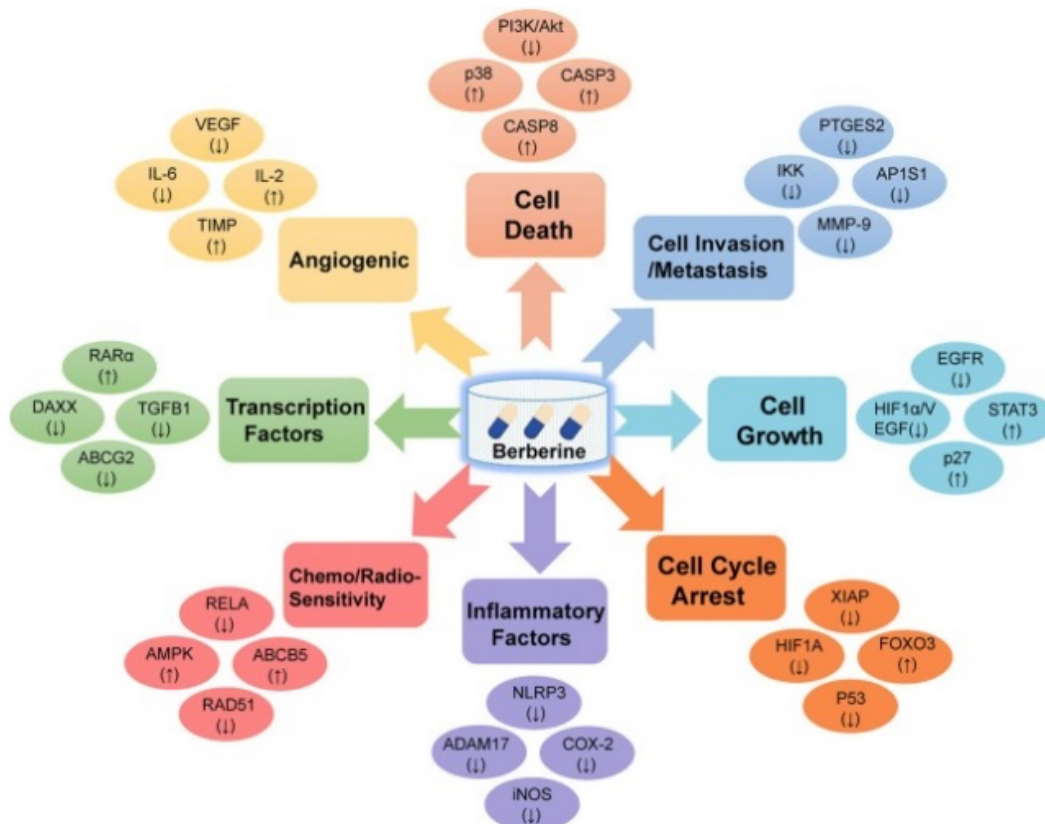


Fig 6. Anti-cancer properties of berberine [30]

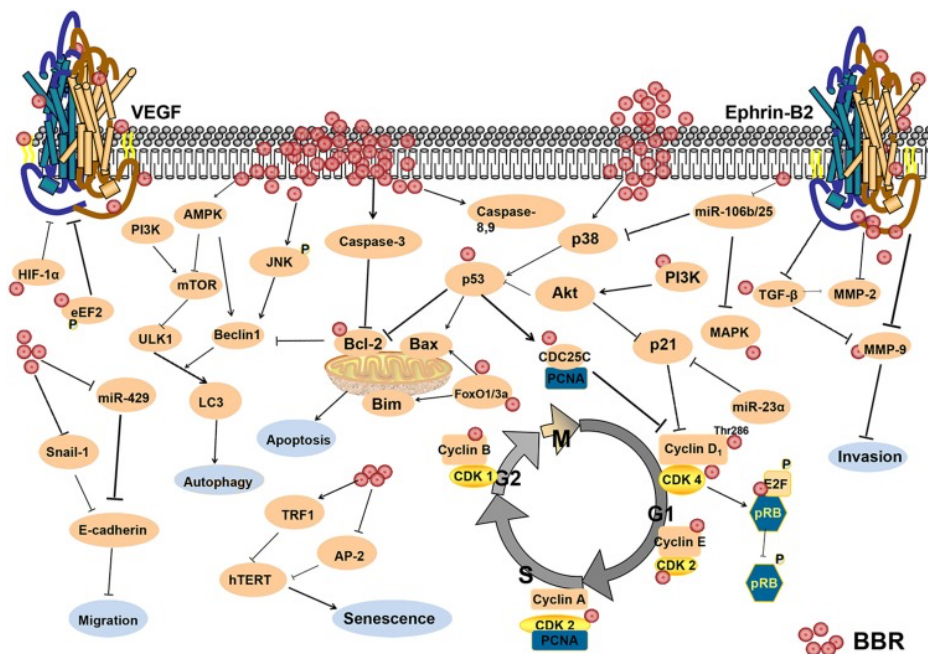


Fig 7. Mechanism of anti-cancer activity of Berberine [31]

Terpene: Terpenes are natural isoprenoid derivatives. Terpenes can be found in plants like thyme, Cannabis, tea (*Melaleuca alternifolia*), Spanish sage (*Salvia lavandulifolia*), citrus fruits like lemon, orange, mandarin [44].

Cannabis (Myrcene): Cannabis is from *Cannabis sativa* plant (Fig 8). Cannabis is most abundant in myrcene. Myrcene can also be found in parley, hops, thyme, and lemongrass [45].

Cannabis has the potential to mitigate cancer

however because of its components which cause undesirable effects, the use of it has been skeptical. The two main cannabinoids in cannabis are Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD) with both of them portraying different pharmacological activities (Fig 9). Utilizing Δ^9 -THC has been associated with some unfavourable effects like tachycardia, anxiety, altered cognitive perception, and psychoactivity that can lead to addiction. Such undesirable effects however are not seen with CBD [46]. CBD has shown potential anticancer properties.



Fig 8. Cannabis plant [45]

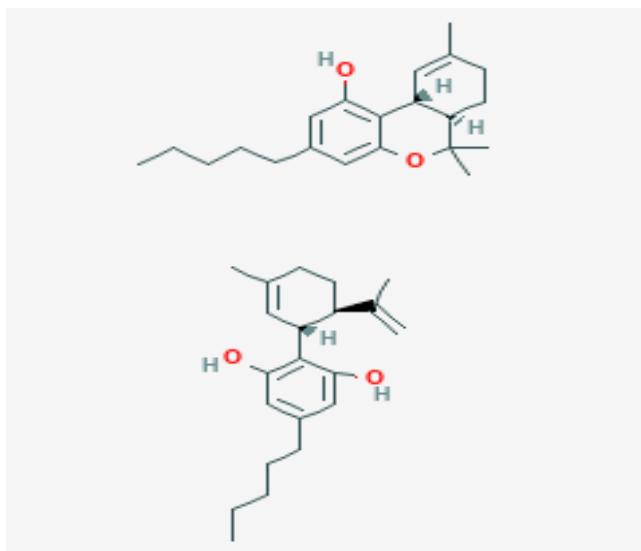


Fig 9. Structure of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) (up) and cannabidiol (CBD) (down) [47]

CBD has been shown to have anticancer effects on several types of cancer such as lung cancer, glioma, thyroid, lymphoma, skin, pancreas, uterus, breast, prostate, and colorectal carcinoma [48]. Over the years more anticancer mechanisms of cannabinoids are emerging, showing their ability to interfere with cancer neovascularization, cancer cell migration, adhesion, invasion, and metastasis [49].

Although CBD has been effective against several types of cancer, most research has been centered on the effect of CBD in glioma cells. Cannabinoids have been shown to influence the death of glioma cells by apoptosis via CB_1 - and CB_2 - and TRPV1-independent stimulation, upregulating cytochrome c, caspase 3, and reducing glutathione. Stimulation of CB_1 - and CB_2 - and TRPV1 receptors upregulated COX-2 in lung and cervical cancers, this is also related to its pro-apoptotic activity. Cancer invasiveness is inhibited by the formation of inhibitory complexes of TIMP-1 with MMP-2 and MMP-9. Cannabinoids drive the intracellular accumulation of ceramide to activate Raf1/ERK signaling leading to the production of damaging cellular reactive oxygen species (ROS). This drives genotoxic stress and apoptosis in glioma cells. Treatment with cannabinoids increased p8,

a stress-regulated protein thereby leading to the inhibition of the Akt/mammalian target of rapamycin (mTOR) cell signalling axis and the activation of caspase cascades. Activation of caspase cascades induced apoptosis in cancer cells. Cannabinoid downregulated the expression of anti-apoptotic protein Bcl-2 which hindered apoptosis while upregulating the expression of apoptosis regulator BAX and cellular tumour antigen p53 (TP53). It can also promote apoptosis through tumour necrosis factor- α (TNF- α) mediated de novo synthesis of ceramide [50].

Endoplasmic reticulum stress-related transcription factors ATF4 and CHOP, and the pseudokinase tribbles homologue 3 (TRIB3) are also targeted by cannabinoids which leads to inhibition of the mammalian target of rapamycin complex 1 (mTORC1) leading to apoptosis via autophagy-mediated cell death. Cannabinoid promoted inhibition of the interaction of TRIB3 with a pro-survival kinase, AKT37, and AKT38. This eventually leads to the death of cancer cells [51].

Asides from glioma cells, in hepatocellular carcinoma cells, cannabinoid also induced endoplasmic reticulum stress-dependent activation of calcium/calmodulin-dependent protein kinase 2 β and AMP-activated protein kinase also leading to cell death. The cannabinoid-

mediated inhibition of AKT promoted the arrest of the cell cycle in cancer cells of breast cancer and melanoma cancer. It also induced apoptosis by decreasing phosphorylation of the pro-apoptotic protein Bcl2-associated agonist of cell death and activation of the cyclin-dependent kinase inhibitory proteins p21 and p27. This resulted in subsequently decreased phosphorylation of the retinoblastoma protein causing the arrest of the cell cycle, then cell death [52].

Cannabinoid achieved its antiangiogenic properties by blocking the activation of the vascular endothelial

growth factor pathway which induces angiogenesis. Vascular endothelial growth factor receptors 1 & 2 are also downregulated by cannabinoids [53]. In human prostate cancer cell lines, CBD downregulated CB₁, CB₂, PSA, VEGF, IL-6, and IL-8 demonstrating its anti-inflammatory activities [54]. These mechanisms of action of CBD are highlighted in Fig 10.

Aside from myrcene, there are other terpenes present in cannabis which include α-pinene, and β-caryophyllene [55].

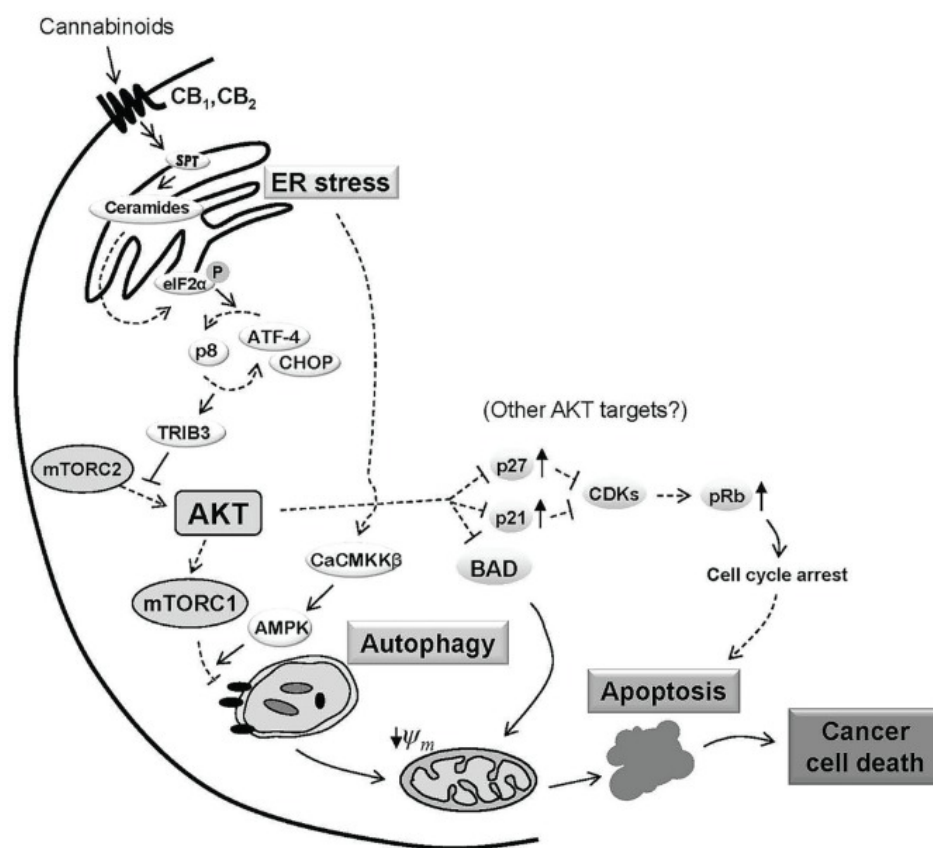


Fig 10. Mechanism of anticancer activity of cannabinoid [56]

Another terpene that has gained attention for its potential in cancer mitigation is lycopene. Lycopene is a tetraterpene. It is part of the carotenoid family of compounds [57]. Lycopene is found mostly in tomatoes [58]. Lycopene’s mechanism in combating cancer includes most noticeably antioxidant properties, obstruction of insulin-like growth factor 1 receptor

signaling pathways, decreased lipid oxidation, inhibition of cancer cell proliferation, apoptosis, increased gap-junctional communication and hindering cell cycle progression. It also inhibits cell invasion, angiogenesis, and metastasis [59].

Other terpenes with anti-cancer prospects are Limonene and Canthardin which are monoterpenes,

Artemism which is a sesquiterpene, Tanshiron 11A, Triptolide, Pseudolanic acid B, Oridorin and Adrographolide which are diterpenes, Celestrol, cucurbitacin, Alisol B, and Pachymic acid which are triterpenes.

Tannin: Tannins are polyphenols with higher molecular weight [60]. Plants in which tannin can be found include barks of Red Angico (*Anadenanthera macrocarpa*),

Jaboticaba (*Myrciaria jaboticaba*) and Umbu (*Spondias tuberosa*) [61]. It can also be found in wattle (*Acacia mearnsii*) [62].

Gallic Acid: Gallic acid is a trihydroxybenzoic acid, also known as 3, 4, 5-trihydroxybenzoic acid. It belongs to the group of hydrolyzable tannins (Fig 11). Gallic acid is present in food such as plums, grapes, mango, gallnuts, cashew nut, hazelnut, berries, walnut, tea, and wine [63].

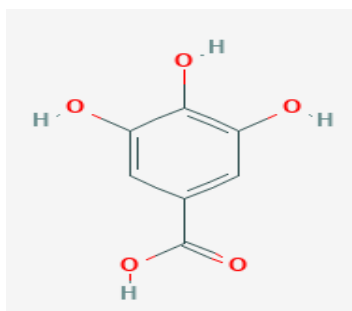


Fig 11. Chemical structure of Gallic acid [64]

Gallic acid and its derivatives are effective against cancer. It has been shown to have the ability to combat various

kinds of cancer like colon cancer, breast cancer, liver cancer, esophageal cancer, leukemia e.t.c

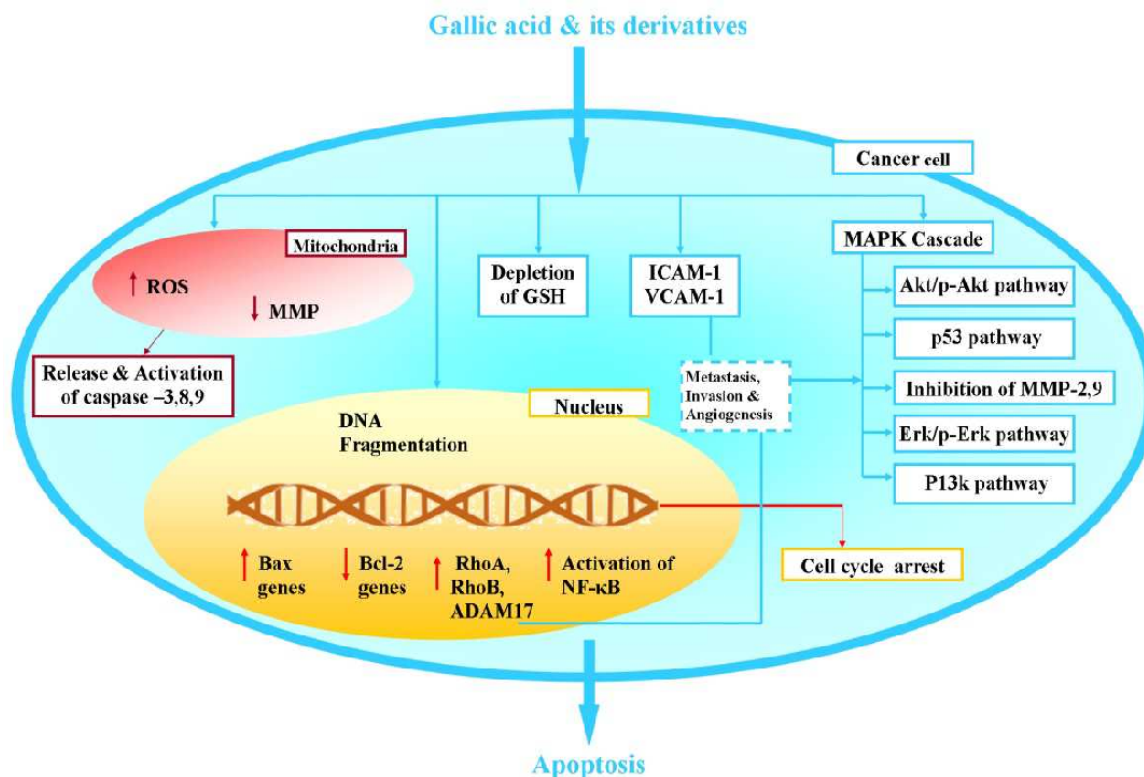


Fig 12. Mechanism of anticancer activity of gallic acid [65]

Studies on the anti-cancer mechanism of gallic acid on human colon adenocarcinoma COLO 205 cells showed fragmentation of DNA to oligonucleosomal fragments after gallic acid treatment [66]. Gallic acid also induced apoptosis of cancer cells. In a study on HCT-15 human colon cancer cells, gallic acid caused the rounding and shrinking of the cell and also detachment from the substratum. These reduced the viability of the cancer cells leading to the death of the cells. The study also showed antiproliferative effect of gallic acid against U-2OS osteosarcoma cells. The levels of p-JNK and p-ERK1/2 kinase decreased while the level of p38 kinase increased after the treatment with gallic acid. This indicated that gallic acid induced apoptosis of osteosarcoma cells through the inactivation of JNK and ERK1/2 kinase pathways and the activation of p38 kinase pathway. CD31 which promotes angiogenesis was significantly less, illustrating the anti-angiogenetic effect of gallic acid in U-2OS cells. GRB2, PI3K, AKT/PKB, PKC, p38, ERK1/2, JNK, NF- κ B p65 were also down-regulated by gallic acid and it inhibited the activities of AKT, IKK, PKC, MMP-2, and MMP-9 proteins [67].

Gallic acid diminished the growth of breast cancer cells by increasing p27 and p21 while decreasing the activity of cyclin A, CDK2, cyclin B1, and cdc2/CDK1. This caused consistent halting of cells at the G2/M phase, therefore, obstructing proliferation [65]. Gallic acid also induced apoptosis by enhancing the cleavage of Poly-ADP-ribose polymerase 1 and promoting mitochondrial membrane depolarization and causing morphological alteration. Gallic acid treatment in studies showed that activated caspase-3, caspase-9, and ROS, elevated Bax expression, and reduced mitochondrial membrane integrity. Overexpression of Bcl-2 in cancer cells and phosphorylation of c-Jun N-terminal protein kinase also occurred [68].

Another study showed cytotoxic effect of gallic acids in leukemia. The study portrayed apoptosis of leukemia cells after treatment with gallic acid. Apoptosis of cells was

coupled with cell cycle arrest at the G0/G1 phase [69]. Gallic acid also caused the inhibition of ribonucleotide reductase [70].

Other tannins that showed anticancer properties are proanthocyanidin, tarragallotannin, and caffetannin [71].

CONCLUSION

Cancer can affect any part of the body and is one of the primary causes of death globally. Radiotherapy, surgery and chemotherapy are currently been utilized in the management of cancer but they have been discovered to have side effects and cannot effectively cure this disease. Bioactive compounds are a very promising focus in the prevention and treatment of cancer. Some of these compounds have been discovered to have positive effects in the treatment of breast cancer, prostate cancer, colon cancer, lung cancer, esophageal cancer, cervical cancer, leukemia, melanoma and glioma cells. These phytochemicals possess diverse mechanisms with which they can be effective against cancer. In this review, the mechanisms of action of some bioactive compounds; genistein, berberine, gallic acid and CBD were outlined which include: induction of apoptosis in the cancer cells by fragmentation of the DNA, preventing angiogenesis, halting the cell cycle and stopping metastasis of the cancer cells, inhibiting cell proliferation. As a result of these mechanisms of action, these bioactive compounds could be great prospects in the development of therapeutic drugs effective in the treatment of different types of cancer. Most of these studies are however *in vitro* studies involving cancer cell cultures therefore, more clinical studies are needed to validate the usefulness of these bioactive compounds in cancer management.

List of Abbreviations: DNA: Deoxyribonucleic acid; NF- κ B: Nuclear factor kappa B; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma-2; MAPK: Mitogen-activated protein

kinase; C/EBP: CCAAT-enhancer-binding proteins; GRP78: Glucose Regulated Protein-78; ATM/ATR: Ataxia telangiectasia mutated (ATM) rad3-related (ATR); Chk: Checkpoint kinase, COX: Cyclooxygenase; Ang-1: Angiopoietin-1; FAK: Focal adhesion kinase; IL: Interleukin; miR: MicroRNAs; Nrf2: Nuclear factor erythroid2-related factor 2; AMPK/mTOR: /mammalian target of rapamycin; TNF α : Tumour necrosis factor- α ; MMP: Metalloproteinase, TGF: Transforming growth factor; MMP: Matrix metalloproteinases; TIMP: Tissue inhibitors of matrix metalloproteinases; CHOP: C/EBP Homologous Protein; ERK: extracellular signal-regulated kinases; JNK-c: Jun N-terminal kinases; MAPK: mitogen-activated protein kinase; MAPKAPK2: MAP kinase activated protein kinase 2

Competing Interests: The authors have no financial interests or conflicts of interest

Authors' Contribution: All authors contributed to this study

Acknowledgments and Funding: No funding was received for this review.

REFERENCES

1. Cancer. Encyclopedia Britannica. [\[https://www.britannica.com/science/cancer-disease\]](https://www.britannica.com/science/cancer-disease) Retrieved 2021.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021, 71(3):209-49. <https://doi.org/10.3322/caac.21660>.
3. Le Large TY, Bijlsma MF, Kazemier G, Van Laarhoven HW, Giovannetti E, Jimenez CR: Key biological processes driving metastatic spread of pancreatic cancer as identified by multi-omics studies. *In Seminars in cancer biology* 2017, 44:153-169, ISSN 1044-579X, Academic Press. <https://doi.org/10.1016/j.semcancer.2017.03.008>.
4. Robinson AD, Eich ML, Varambally S: Dysregulation of de novo nucleotide biosynthetic pathway enzymes in cancer and targeting opportunities. *Cancer Lett* 2020, 470:134-40. <https://doi.org/10.1016/j.canlet.2019.11.013>.
5. Zakraoui O, Marcinkiewicz C, Aloui Z, Othman H, Grépin R, Haoues M, Essafi M, Srairi-Abid N, Gasmi A, Karoui H, Pagès G: Lebein, a snake venom disintegrin, suppresses human colon cancer cells proliferation and tumor-induced angiogenesis through cell cycle arrest, apoptosis induction and inhibition of VEGF expression. *Molecular carcinogenesis* 2017, 56(1):18-35. <https://doi.org/10.1002/mc.22470>.
6. Pierotti MA, Frattini M, Molinari F, Sozzi G, Croce CM: Oncogenes. *Holland-Frei Can Med*. 2016, 1-22.
7. Liu J, Charles Lin P, Zhou BP: Inflammation fuels tumor progress and metastasis. *Curr Pharm Des* 2015, 21(21):3032-40.
8. Subramaniam S, Selvaduray KR, Radhakrishnan AK: Bioactive compounds: natural defense against cancer? *Biomolecules* 2019, 9(12): 758. <https://doi.org/10.3390/biom9120758>.
9. Kopustinskiene DM, Jakstas V, Savickas A, Bernatoniene J: Flavonoids as anticancer agents. *Nutrients* 2020, 12(2): 457. <https://doi.org/10.3390/nu12020457>.
10. National Center for Biotechnology Information (NCBI). PubChem Compound Summary for CID 5280961, Genistein. [<https://pubchem.ncbi.nlm.nih.gov/compound/Genistein>]. Retrieved Mar. 30, 2021.
11. Forslund LC, Andersson HC: Phytoestrogens in foods on the Nordic market: A literature review on occurrence and levels. 2017, 541. ISBN 978-92-893-5047.
12. Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, Nabavi SF, Devi KP, Loizzo MR, Tundis R, Nabavi SM: Genistein and cancer: current status, challenges, and future directions. *Adv Nutr* 2015, 6(4): 408-19. <https://doi.org/10.3945/an.114.008052>.
13. Hsiao YC, Peng SF, Lai KC, Liao CL, Huang YP, Lin CC, Lin ML, Liu KC, Tsai CC, Ma YS, Chung J: Genistein induces apoptosis in vitro and has antitumor activity against human leukemia HL-60 cancer cell xenograft growth in vivo. *Environ Toxicol* 2019, 34(4): 443-56. <https://doi.org/10.1002/tox.22698>.
14. Shafiee G, Saidijam M, Tavilani H, Ghasemkhani N, Khodadadi I: Genistein induces apoptosis and inhibits proliferation of HT29 colon cancer cells. *Int J Mol Cell Med* 2016, 5(3): 178-191.
15. Zhou P, Wang C, Hu Z, Chen W, Qi W, Li A: Genistein induces apoptosis of colon cancer cells by reversal of epithelial-to-mesenchymal via a Notch1/NF- κ B/slugg/E-cadherin pathway. *BMC cancer* 2017, 17(1): 1-10. <https://doi.org/10.1186/s12885-017-3829-9>.

16. Ono M, Ejima K, Higuchi T, Takeshima M, Wakimoto R, Nakano S: Equol enhances apoptosis-inducing activity of genistein by increasing Bax/Bcl-xL expression ratio in MCF-7 human breast cancer cells. *Nutr. Cancer* 2017, 69(8): 1300-7. <https://doi.org/10.1080/01635581.2017.1367945>.
17. Heo JR, Lee GA, Kim GS, Hwang KA, Choi KC: Phytochemical-induced reactive oxygen species and endoplasmic reticulum stress-mediated apoptosis and differentiation in malignant melanoma cells. *Phytomedicine* 2018, 39:100-10. <https://doi.org/10.1016/j.phymed.2017.12.006>.
18. Li S, Li J, Dai W, Zhang Q, Feng J, Wu L, Liu T, Yu Q, Xu S, Wang W, Lu X: Genistein suppresses aerobic glycolysis and induces hepatocellular carcinoma cell death. *Br J Cancer* 2017, 117(10): 1518-28. <https://doi.org/10.1038/bjc.2017.323>.
19. Abari AH, Tayebi M: Bioconversion of genistein to orobol by *Bacillus subtilis* spore displayed tyrosinase and monitoring the anticancer effects of orobol on MCF-7 breast cancer cells. *Biotechnol Bioprocess Eng* 2019, 24(3): 507-12. <https://doi.org/10.1007/s12257-019-0067-9>.
20. Smolińska E, Moskot M, Jakóbkiewicz-Banecka J, Węgrzyn G, Banecki B, Szczerkowska-Dobosz A, Purzycka-Bohdan D, Gabig-Cimińska M: Molecular action of isoflavone genistein in the human epithelial cell line HaCaT. *PloS one* 2018, 13(2): e0192297. <https://doi.org/10.1371/journal.pone.0192297>.
21. Tuli HS, Tuorkey MJ, Thakral F, Sak K, Kumar M, Sharma AK, Sharma U, Jain A, Aggarwal V, Bishayee A: Molecular mechanisms of action of genistein in cancer: Recent advances. *Frontiers in Pharmacology* 2019, 1336. <https://doi.org/10.3389/fphar.2019.01336>.
22. Xiao X, Liu Z, Wang R, Wang J, Zhang S, Cai X, Wu K, Bergan RC, Xu L, Fan D: Genistein suppresses FLT4 and inhibits human colorectal cancer metastasis. *Oncotarget* 2015, 6(5): 3225. <https://dx.doi.org/10.18632/oncotarget.3064>.
23. Varinska L, Gal P, Mojzisoava G, Mirossay L, Mojzis J: Soy and breast cancer: focus on angiogenesis. *International Journal of Molecular Sciences* 2015, 16(5): 11728-49. <https://doi.org/10.3390/ijms160511728>.
24. Raina R, Afroze N, Sundaram MK, Haque S, Bajbouj K, Hamad M, Hussain A: Chrysin inhibits propagation of HeLa cells by attenuating cell survival and inducing apoptotic pathways. *Eur Rev Med Pharmacol Sci* 2021, 25:2206-20.
25. Gao J, Xia R, Chen J, Gao J, Luo X, Ke C, Ren C, Li J, Mi Y: Inhibition of esophageal-carcinoma cell proliferation by genistein via suppression of JAK1/2-STAT3 and AKT/MDM2/p53 signaling pathways. *Aging (Albany NY)* 2020, 12(7): 6240-6259. <https://dx.doi.org/10.18632/aging.103019>.
26. Cui S, Wang J, Wu Q, Qian J, Yang C, Bo P: Genistein inhibits the growth and regulates the migration and invasion abilities of melanoma cells via the FAK/paxillin and MAPK pathways. *Oncotarget* 2017, 8(13): 21674. <https://dx.doi.org/10.18632/oncotarget.15535>.
27. Wang J, Jiang Y, Wang B, Zhang N: A review on analytical methods for natural berberine alkaloids. *J Sep Sci* 2019, 42(9): 1794-815. <https://doi.org/10.1002/jssc.201800952>.
28. PCOS and Berberine: What Women Should Know. *Very Well Health*. <https://www.verywellhealth.com/pcos-and-berberine-4136324>. Retrieved 2020.
29. National Center for Biotechnology Information (NCBI). PubChem Compound Summary for CID 2353, Berberine. [<https://pubchem.ncbi.nlm.nih.gov/compound/Berberine>] Retrieved March 29, 2021.
30. Guo P, Cai C, Wu X, Fan X, Huang W, Zhou J, Wu Q, Huang Y, Zhao W, Zhang F, Wang Q: An insight into the molecular mechanism of berberine towards multiple cancer types through systems pharmacology. *Frontiers in pharmacology* 2019:857. <https://dx.doi.org/10.3389/fphar.2019.00857>.
31. Wang Y, Liu Y, Du X, Ma H, Yao J: The anti-cancer mechanisms of berberine: A review. *Cancer management and research* 2020,12:695. <https://dx.doi.org/10.2147/CMAR.S242329>.
32. Jin H, Jin X, Cao B, Wang W: Berberine affects osteosarcoma via downregulating the caspase-1/IL-1 β signaling axis. *Oncology reports* 2017, 37(2): 729-36. <https://doi.org/10.3892/or.2016.5327>
33. Chu SC, Yu CC, Hsu LS, Chen KS, Su MY, Chen PN: Berberine reverses epithelial-to-mesenchymal transition and inhibits metastasis and tumor-induced angiogenesis in human cervical cancer cells. *Mol Pharmacol* 2014, 86(6): 609-23. <https://doi.org/10.1124/mol.114.094037>.
34. McCubrey JA, Lertpiriyapong K, Steelman LS, Abrams SL, Yang LV, Murata RM, Rosalen PL, Scalisi A, Neri LM, Cocco L, Ratti S: Effects of resveratrol, curcumin, berberine and other nutraceuticals on aging, cancer development, cancer stem cells and microRNAs. *Aging (Albany NY)* 2017, 9(6): 1477. <https://dx.doi.org/10.18632/aging.101250>.

35. La X, Zhang L, Li Z, Yang P, Wang Y: Berberine-induced autophagic cell death by elevating GRP78 levels in cancer cells. *Oncotarget* 2017, 8(13): 20909. <https://dx.doi.org/10.18632/oncotarget.14959>.
36. Xu Z, Feng W, Shen Q, Yu N, Yu K, Wang S, Chen Z, Shioda S, Guo Y: Rhizoma coptidis and berberine as a natural drug to combat aging and aging-related diseases via anti-oxidation and AMPK activation. *Aging Dis* 2017, 8(6): 760. <https://dx.doi.org/10.14336/afad.2016.0620>.
37. Wang Y, Liu Y, Du X, Ma H, Yao J: The anti-cancer mechanisms of berberine: a review. *Cancer Manag Res* 2020, 12:695. <https://dx.doi.org/10.21472/FCMAR.S242329>.
38. Kim JH, Ryu AR, Kang MJ, Lee MY: Berberine-induced changes in protein expression and antioxidant enzymes in melanoma cells. *Mol Cell Toxicol* 2016, 12(1): 53-61. <https://doi.org/10.1007/s13273-016-0008-z>.
39. Mao L, Chen Q, Gong K, Xu X, Xie Y, Zhang W, Cao H, Hu T, Hong X, Zhan YY: Berberine decelerates glucose metabolism via suppression of mTOR-dependent HIF-1 α protein synthesis in colon cancer cells. *Oncology reports* 2018, 39(5): 2436-42. <https://doi.org/10.3892/or.2018.6318>.
40. Hamsa TP, Kuttan G: Antiangiogenic activity of berberine is mediated through the downregulation of hypoxia-inducible factor-1, VEGF, and proinflammatory mediators. *Drug and Chemical Toxicology* 2012, 35(1):57-70. <https://doi.org/10.3109/01480545.2011.589437>.
41. Li X, Zhang A, Sun H, Liu Z, Zhang T, Qiu S, Liu L, Wang X: Metabolic characterization and pathway analysis of berberine protects against prostate cancer. *Oncotarget* 2017, 8(39): 65022. <https://dx.doi.org/10.18632/oncotarget.17531>.
42. Okubo S, Uto T, Goto A, Tanaka H, Nishioku T, Yamada K, Shoyama Y: Berberine induces apoptotic cell death via activation of caspase-3 and -8 in HL-60 human leukemia cells: nuclear localization and structure-activity relationships. *Am J Chinese Med* 2017, 45(7): 1497-511. <https://doi.org/10.1142/S0192415X17500811>.
43. Li J, Liu F, Jiang S, Liu J, Chen X, Zhang S, Zhao H: Berberine hydrochloride inhibits cell proliferation and promotes apoptosis of non-small cell lung cancer via the suppression of the MMP2 and Bcl-2/Bax signaling pathways. *Oncol. Lett* 2018, 15(5): 7409-14. <https://doi.org/10.3892/ol.2018.8249>.
44. Medicinal Plants. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7120914/> Retrieved Nov 12, 2019.
45. Eichhorn Bilodeau S, Wu BS, Rufyikiri AS, MacPherson S, Lefsrud M: An update on plant photobiology and implications for cannabis production. *Front Plant Sci* 2019, 10: 296. <https://doi.org/10.3389/fpls.2019.00296>.
46. Colizzi M, Bhattacharyya S: Does cannabis composition matter? Differential effects of delta-9-tetrahydrocannabinol and cannabidiol on human cognition. *Curr Addict Rep* 2017, 4(2):62-74. <https://doi.org/10.1007/s40429-017-0142-2>.
47. National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 9852188, Cannabinoids. <https://pubchem.ncbi.nlm.nih.gov/compound/Cannabinoids> Retrieved March 30, 2021.
48. Kovalchuk O, Kovalchuk I: Cannabinoids as anticancer therapeutic agents. *Cell Cycle* 2020,19(9):961-89. <https://doi.org/10.1080/15384101.2020.1742952>.
49. Pellati F, Borgonetti V, Brighenti V, Biagi M, Benvenuti S, Corsi L: Cannabis sativa L. and nonpsychoactive cannabinoids: their chemistry and role against oxidative stress, inflammation, and cancer. *BioMed Res Int* 2018, 2018. Article ID: 1691428. <https://doi.org/10.1155/2018/1691428>.
50. Desprez PY, Murase R, Limbad C, Woo RW, Adrados I, Weithenthaler K, Soroceanu L, Salomonis N, McAllister SD: Cannabidiol Treatment Results in a Common Gene Expression Response Across Aggressive Cancer Cells from Various Origins. *Cannabis Cannabinoid Res* 2021, 6(2): 148-55. <https://doi.org/10.1089/can.2019.0081>.
51. Afrin F, Chi M, Eamens AL, Duchatel RJ, Douglas AM, Schneider J, Gedye C, Woldu AS, Dun MD: Can hemp help? Low-THC cannabis and non-THC cannabinoids for the treatment of cancer. *Cancers* 2020, 12(4):1033. <https://doi.org/10.3390/cancers12041033>.
52. Velasco G, Sánchez C, Guzmán M: Anticancer mechanisms of cannabinoids. *Curr Oncol* 2016, 23(s1):23-32. <https://doi.org/10.3747/co.23.3080>.
53. Sharma M, Hudson JB, Adomat H, Guns E, Cox ME: In vitro anticancer activity of plant-derived cannabidiol on prostate cancer cell lines. *Pharmacology & Pharmacy* 2014, 5(8):806. <http://dx.doi.org/10.4236/pp.2014.58091>.
54. Han CC, Wan FS: New insights into the role of endoplasmic reticulum stress in breast cancer metastasis. *J Breast Cancer* 2018, 21(4):354-62. <https://doi.org/10.4048/jbc.2018.21.e51>.

55. Honarmand M, Namazi F, Mohammadi A, Nazifi S: Can cannabidiol inhibit angiogenesis in colon cancer? *Comp Clin Path* 2019, 28(1):165-72.
<https://doi.org/10.1007/s00580-018-2810-6>.
56. Morales P, Jagerovic N: Antitumor cannabinoid chemotypes: Structural insights. *Front Pharmacol* 2019, 10:621.
<https://doi.org/10.3389/fphar.2019.00621>.
57. Asadi S, Pirsia S: Production of biodegradable film based on polylactic acid, modified with lycopene pigment and TiO₂ and studying its physicochemical properties. *J Polym Environ* 2020, 28(2):433-44.
<https://doi.org/10.1007/s10924-019-01618-5>.
58. Costa-Rodrigues J, Pinho O, Monteiro PR: Can lycopene be considered an effective protection against cardiovascular disease? *Food Chem* 2018, 245:1148-53.
<https://doi.org/10.1016/j.foodchem.2017.11.055>.
59. Ono M, Takeshima M, Nakano S: Mechanism of the anticancer effect of lycopene (tetraterpenoids). *The Enzymes* 2015, 37:139-66.
<https://doi.org/10.1016/bs.enz.2015.06.002>.
60. Nguela JM, Poncet-Legrand C, Sieczkowski N, Vernhet A: Interactions of grape tannins and wine polyphenols with a yeast protein extract, mannoproteins and β -glucan. *Food Chem* 2016, 210:671-82.
<https://doi.org/10.1016/j.foodchem.2016.04.050>.
61. Martins RO, Gomes IC, Telles AD, Kato L, Souza PS, Chaves AR: Molecularly imprinted polymer as solid phase extraction phase for condensed tannin determination from Brazilian natural sources. *J Chromatogr A* 2020, 1620:460977.
<https://doi.org/10.1016/j.chroma.2020.460977>.
62. Avila AS, Zambom MA, Faccenda A, Fischer ML, Anschau FA, Venturini T, Tinini RC, Dessbesell JG, Faciola AP: Effects of black wattle (*Acacia mearnsii*) condensed tannins on intake, protozoa population, ruminal fermentation, and nutrient digestibility in Jersey steers. *Animals* 2020, 10(6):1011.
<https://doi.org/10.3390/ani10061011>.
63. Daglia M, Di Lorenzo A, F Nabavi S, S Talas Z, M Nabavi S: Polyphenols: well beyond the antioxidant capacity: gallic acid and related compounds as neuroprotective agents: you are what you eat!. *Curr Pharma Biotechnol* 2014, 15(4):362-72.
64. National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 370, Gallic acid.
<https://pubchem.ncbi.nlm.nih.gov/compound/Gallic-acid>
Retrieved March 30, 2021.
65. Subramanian AP, John AA, Vellayappan MV, Balaji A, Jaganathan SK, Supriyanto E, Yusof M: Gallic acid: prospects and molecular mechanisms of its anticancer activity. *RSC Adv* 2015, 5(45):35608-21.
<https://doi.org/10.1039/C5RA02727F>.
66. Weng SW, Hsu SC, Liu HC, Ji BC, Lien JC, Yu FS, Liu KC, Lai KC, Lin JP, Chung JG: Gallic acid induces DNA damage and inhibits DNA repair-associated protein expression in human oral cancer SCC-4 cells. *Anticancer Res* 2015, 35(4):2077-84.
67. Kuo CL, Lai KC, Ma YS, Weng SW, Lin JP, Chung JG: Gallic acid inhibits migration and invasion of SCC-4 human oral cancer cells through actions of NF- κ B, Ras and matrix metalloproteinase-2 and-9. *Oncol Rep* 2014, 32(1):355-61.
<https://doi.org/10.3892/or.2014.3209>.
68. Lu YC, Lin ML, Su HL, Chen SS: ER-dependent Ca⁺⁺-mediated cytosolic ROS as an effector for induction of mitochondrial apoptotic and ATM-JNK signal pathways in gallic acid-treated human oral cancer cells. *Anticancer Res* 2016, 36(2):697-705.
69. Lee HL, Lin CS, Kao SH, Chou MC: Gallic acid induces G1 phase arrest and apoptosis of triple-negative breast cancer cell MDA-MB-231 via p38 mitogen-activated protein kinase/p21/p27 axis. *Anti-cancer drugs* 2017, 28(10):1150-6.
<https://doi.org/10.1097/cad.0000000000000565>
70. Velderrain-Rodríguez G, Torres-Moreno H, Villegas-Ochoa MA, Ayala-Zavala JF, Robles-Zepeda RE, Wall-Medrano A, González-Aguilar GA: Gallic acid content and an antioxidant mechanism are responsible for the antiproliferative activity of 'Ataulfo' mango peel on LS180 cells. *Molecules* 2018, 23(3):695.
<https://doi.org/10.3390/molecules23030695>.
71. Muniyandi K, George E, Sathyanarayanan S, George BP, Abrahamse H, Thamburaj S, Thangaraj P: Phenolics, tannins, flavonoids and anthocyanins contents influenced antioxidant and anticancer activities of Rubus fruits from Western Ghats, India. *Food Sci Hum Wellness* 2019, 8(1):73-81.
<https://doi.org/10.1016/j.fshw.2019.03.005>.